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EXAMINER	
PALENIK, JEFFREY T	

ART UNIT	PAPER NUMBER
1615	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/540,139	COLOMBO ET AL.	
	Examiner	Art Unit	
	Jeffrey T. Palenik	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 October 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10 and 21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

STATUS OF THE APPLICATION

Applicants' amendments and remarks filed 5 October 2009 are acknowledged and entered on the record. The Examiner acknowledges the following:

No claims have been added or canceled.

Claim 1 has been amended to merely clarify the language. As such, no new matter is considered to have been added.

Thus, claims 1-10 and 21 continue to represent all claims currently under consideration.

INFORMATION DISCLOSURE STATEMENT

No new Information Disclosure Statements (IDS) have been submitted for consideration.

WITHDRAWN OBJECTIONS/REJECTIONS

Rejection under 35 USC 112

Applicants' remarks to claim 6 concerning the written description rejection, under 35 USC 112, first paragraph, have been fully reconsidered and are persuasive. The rejection stands **withdrawn**. However, for the purposes of examination on the merits, and pursuant to MPEP §§2111 and 2123, the definition provided for "dielectric material" in the instant specification is broadly and reasonably interpreted by the Examiner for all that it would

convey to the ordinarily skilled artisan. Said description is so broad as to include any material which may be heated via a microwave, including water.

Applicants' remarks concerning the scope of enablement rejection to claims 1-10, under 35 USC 112, first paragraph, have been fully considered and are persuasive. Thus, said rejections have been **withdrawn**.

Applicants' remarks concerning the scope of indefiniteness rejection to claim 1, under 35 USC 112, second paragraph, have been fully considered and are persuasive. Thus, said rejections have been **withdrawn**.

MAINTAINED REJECTIONS

The following rejections are maintained from the previous Office Correspondence dated 12 May 2009 since either the grounds or art on which they were previously set forth continues to read on the amended limitations.

CLAIM REJECTIONS - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3, 8 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of Aoki (EP 1 308 156 A1) and Miyamoto et al. (USPN 6,462,093).

The instantly amended claim 1 is drawn to a process for preparing a composite containing a drug in an organic carrier. Said method comprises first mixing a drug with an organic carrier, wherein said carrier is selected from a water-soluble complexing agent and water-insoluble cross-linked polymer. Second, the mixture is subjected to microwave irradiation such that the temperature of the mixture is increased above the melting point of the drug and maintained for at least five minutes. That the method forms a composite containing the drug dispersed throughout the carrier is present in the amorphous form equal to or greater than 50% by weight of the total amount of the drug, as recited in claim 1 is considered by the Examiner as being the expected result of performing the instantly claimed method. Thus, with regard said limitation, until some material difference in the properties of the method are

demonstrated, said product limitation is considered by the Examiner to be directed toward the method, which is instantly claimed. Claims 2 and 3 recite limitations to the method such that the drug/carrier mixture is further mixed with a solvent such as water, to form a wet mixture prior to heating. Claim 8 recites that the microwave heating step of claim 1 is carried out within the power range of 100-5,000 Watts and for a period of time up to 120 minutes. Claim 10 recites that the drug which is used in the method is sparingly soluble (e.g. difficult to dissolve) in water.

Aoki teaches the preparation of a solid dispersion composition comprising a slightly water-soluble medicament blended with a water-soluble polymer, exposed to microwaves ¶[0008]. The medicament/polymer mixture is further expressly taught as being combined with water in an amount which preferably ranges from 0.8-30% by weight ¶[0011]. Slightly-soluble medicaments such as nifedipine are taught in ¶[0008] and the Examples. Embodiments of the water-soluble polymer are taught in ¶[0019] and include polymers such as hydroxypropyl methylcellulose-acetate succinate (HPMC-AS). The organic water-soluble polymer is further taught as being in particle form. Paragraph [0014] teaches that the components may be combined to form a wet-granulated composition. Lastly, microwave exposure to melt the slightly soluble medicament and/or the water-soluble polymer to form the solid dispersion is taught as occurring for a maximum time of four minutes (Fig. 1 and 2, ¶[0011]). A microwave power level of 630 watts is expressly taught as being used for nifedipine mixtures (see Examples).

Aoki does not expressly teach that the temperature achieved during the microwave heating step, is above the melting point of the slightly soluble medicament, nor is it taught that microwaving occurs for longer than four minutes.

Miyamoto et al. teaches a process for producing a solid dispersion of a sparingly water-soluble substance which comprises subjecting said sparingly water-soluble substance, an amorphous state-inducing agent and an amorphous state-stabilizing agent to high-frequency heating (Abstract). The mixture of the aforementioned three ingredients allows for the sparingly water-soluble substance to be made amorphous and dispersed within its carrier at a lower temperature. Combining the sparingly water-soluble substance and the amorphous state-inducing agent is taught as a means for achieving a depressed melting point temperature (i.e. one which is below that of either the substance or the agent), thereby allowing the mixture to be preferably heated at a temperature which is not more than the melting point of the sparingly water-soluble medical substance (col. 4, lines 30-53 and col. 6, lines 27-43). Examples 1 and 4 expressly teach the solid state dispersion of nifedipine within an organic carrier. Example 1 teaches the mixture of five grams (e.g. 5 mL) of water with 10 g of nifedipine, and 20 g of hydroxypropyl methylcellulose-acetate succinate (HPMC-AS). Such a mixture was demonstrated by the teachings of Aoki. However, Miyamoto further adds 10 g of the amorphous state-inducing agent, succinic acid, to the formulation, thereby depressing the melting point temperature of the mixture. Example 4, which uses the wet granulation formulation of Example 1, teaches heating the mixture to 160°C for 20 minutes using a microwave set to 700 watts.

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to have devised the instantly claimed method and achieved the resulting composition by adding an agent such as succinic acid (e.g. an amorphous state-inducing agent) to the formulation of Aoki and increasing the period of microwave exposure time. The ordinarily skilled artisan would have been highly motivated to do adjust the method (i.e. extend the exposure time), particularly in view of the fact that Aoki and Miyamoto both expressly teach the formation of wet granulated compositions comprising nifedipine and HPMC-AS as well as irradiating said compositions via microwave radiation. The teachings of Miyamoto suggest that further combining the mixture with an amorphous state-inducing agent such as succinic acid not only lowers the melting point temperature of the slightly soluble medicament, but also enables the mixture to be exposed to higher wattages of microwave radiation for longer periods of time.

Based on the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, alone or in combination, especially in the absence of evidence to the contrary.

Claims 4, 5, 9 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miyamoto et al. as set forth above with respect to claims 1-3.

The method of claims 1-3 is further limited by claim 4 such that the water is recited as being added to the drug/carrier mixture ranging from 0.1-5.0 mL water/gram of drug/carrier

mix. The limitation recited by claim 5 states that application of the oscillating EM field occurs at a pressure of 1-20 bar. Claim 9 further limits the cross-linked polymer recited in claim 1 whereas claim 21 further limits the water-soluble complexing agents.

The teachings of Miyamoto are discussed above. Examples 1 and 4, in particular teach the use of HPMC-AS as the amorphous state-stabilizing agent. Miyamoto also expressly teaches cross-linked polyvinylpyrrolidone (e.g. crospovidone) as well as α-, β-, and γ-cyclodextrins as functionally equivalent amorphous state-stabilizing agents (col. 5, lines 18-26, 45 and 46), thereby teaching the limitations of claims 9 and 21. The cyclodextrins are preferably taught as being functionally equivalent to HPMC-AS (col. 5, line 66 to col. 6, line 3). The limitation of claim 4 is expressly taught by Examples 1 and 4, whereby the amount of water (e.g. 5 grams or 5 mL) admixed with the drug (e.g. 10 grams nifedipine), the amorphous state-stabilizing agent (e.g. 20 grams HPMC-AS) and amorphous state-inducing agent (e.g. 10 grams succinic acid) results in a wet granulated mixture of about 0.125 mL water per gram of dry ingredient. Regarding the limitation of claim 5, it is broadly and reasonably interpreted by the Examiner as the method being performed at standard atmospheric pressure. Standard atmospheric pressure is well known in the art as being: 1 atmospheres, which is equivalent to about 1.01325 bar. Though the teachings of Miyamoto are silent as to the pressure at which the method is performed, save for the drying step of Example 2, it is concluded, absent evidence to the contrary that the method is performed in an environment incorporating standard atmospheric pressure (i.e. a lab).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to have substituted either crospovidone or a cyclodextrin compound into the method of Miyamoto for HPMC-AS, which is expressly taught. The ordinarily skilled artisan would have been highly motivated to make the aforementioned substitution, especially for α-, β-, or γ-cyclodextrin, particularly since the cyclodextrin compounds are taught as preferable and equivalent alternatives for HPMC-AS (col. 5, line 66 to col. 6, line 3).

Based on the teachings of the reference, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, alone or in combination, especially in the absence of evidence to the contrary.

Claims 6 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of Miyamoto et al. and Aoki et al. as set forth above with respect to claim 1 in combination with Lautenschläger (USPN 5,447,077).

The instant claim 6 recites that the method of claim 1 is performed using a container comprised of a dielectric material having a coupling capacity with microwaves. Claim 7 recites that said material is polytetrafluoroethylene loaded with graphite (e.g. Weflon®).

The teachings to both Miyamoto and Aoki are discussed above. Though it is inherently concluded that the methods to both are performed using a microwave-conducive

container, neither reference expressly discusses from what material said container is constructed.

Lautenschläger teaches a device for the evaporation treatment of preferably liquid substances in a container having a preferably microwave-operated heating appliance (Abstract). Figure 23 shows a vertical partial cross-section of the heating area as well as the holder for one or more containers. The container itself is identified as item (6). Lautenschläger teaches that said container(s) are preferably constructed from a microwave-permeable plastic material, preferably polytetrafluoroethylene (PTFE) and that such plastics preferably contain microwave-absorbing particles such as graphite (e.g. Weflon) (col. 8, lines 25-41 and col. 20, lines 8-16).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to have used a container constructed of Weflon® with either of the methods of Miyamoto or Aoki particularly since Lautenschläger expressly teaches that the material is constructed from both a microwave-permeable material as well as a material which impedes microwaves, which expressly suggests that the manufacture of the material maybe advantageously adjusted to manage the heat of the microwaved mixture (col. 20, lines 4-7).

Based on the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art

at the time the invention was made, as evidenced by the references, alone or in combination, especially in the absence of evidence to the contrary.

RESPONSE TO ARGUMENTS

Applicants' arguments with regard to the rejection of claims 1-10 and 21 under 35 USC 103(a) as being unpatentable over the combined teachings of Aoki et al., Miyamoto et al. and Lautenschläger have been fully considered but they are not persuasive.

Applicants argue each of the forgoing rejections on the grounds that the combined teachings of Aoki et al. and Miyamoto et al. (e.g. the basis for each rejection) do not teach each and every one of the limitations of the recited claims. The crux of Applicants' argument is that neither of the references discloses that the microwave irradiation which occurs is modulated to increase the temperature of the mixture to a temperature greater than the melting temperature of the drug and then maintained at said temperature for at least five minutes, as instantly claimed. It is further alleged that the combined teachings do not describe achieving the instantly claimed drug composite such that after microwaving the mixture, the drug is dispersed both inside of the organic carrier particles as well as on the external surface of the particles.

In response to Applicants' arguments that the references fail to show certain features of Applicants' invention, it is noted that the features upon which applicant relies (i.e., "the melting point of the drug" and "the drug") are not recited in the rejected claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

This argument is similarly applied to Applicants' remarks concerning the discussion of Examples 5 and 6, discussed in the instant specification.

With respect to Applicants' arguments concerning the instantly claimed method, the combined references expressly teach forming a composite comprised of the sparingly soluble drug and organic carrier as instantly claimed in addition to further combining it with an amorphous state-inducing agent (e.g. HPMCAS). The latter agent is expressly taught as depressing the melting point temperature of the drug/carrier mixture such that when heat is applied via microwave, the newly achieved melting points for both the drug and the carrier are overcome and the composition is reduced to an amorphous state. Concerning the term "amorphous" in light of achieving an amorphous state, *Hawley's Condensed Chemical Dictionary* (13th Ed.), defines the term as a substance which is "[n]oncrystalline" and "having no molecular lattice structure, which is characteristic of the solid state. All liquids are amorphous." Since the references expressly teach adding the HPMCAS prior to heating the composite via microwave, it is interpreted by the Examiner that the agent is added to the mixture in order to achieve a lower melting point at which the solid states of both the drug and carrier are overcome in order to achieve an amorphous or liquid (e.g. melted) state.

Concerning Applicants' Examples 5 and 6, as mentioned above, both have been reconsidered in light of the remarks. While the limitations of the specification have not been read into the instant claims, the arguments made are considered to be unpersuasive since the specific Examples do not compare the instant invention to the modifications taught and suggested by the combined teachings of Aoki and Miyamoto.

Lastly, since the instantly claimed method is read upon by the art of record, it is further considered by the Examiner that the product achieved by the method of the art, namely the dispersion of the drug within and on the surface of the organic carrier, necessarily results, absent a clear showing of evidence to the contrary (MPEP §§2112.02 and 2111.04).

For these reasons, Applicants' arguments are found unpersuasive. Said rejections are therefore **maintained**.

All claims under consideration remain rejected; no claims are allowed.

CONCLUSION

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

CORRESPONDENCE

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey T. Palenik whose telephone number is (571) 270-1966. The examiner can normally be reached on 7:30 am - 5:00 pm; M-F (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert A. Wax can be reached on (571) 272-0623. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Jeffrey T. Palenik/
Examiner, Art Unit 1615

/Robert A. Wax/
Supervisory Patent Examiner, Art Unit 1615